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1 RECORD OF ORAL HEARING

2 UNITED STATES PATENT AND TRADEMARK OFFICE

3
4 BEFORE THE BOARD OF PATENT APPEALS
5 AND INTERFERENCES
6

7 *Ex Parte* H. WILLIAM BOSCH, KEVIN D. OSTRANDER
8 and EUGENE R. COOPER
9

10 Appeal 2008-1806
11 Application 09/190,138
12 Technology Center 1600
13

14 Oral Hearing Held: June 10, 2008
15

16 Before TONI R. SCHEINER, DEMETRA J. MILLS, and
17 LORA M. GREEN, *Administrative Patent Judges*.

18 ON BEHALF OF THE APPELLANT:

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P R O C E E D I N G S

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JUDGE SCHEINER: As we go on.

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COURT REPORTER: The spelling of the last name, sir.

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MR. REID: Certainly. It's R-e-i-d.

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COURT REPORTER: Thank you.

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MR. REID: Well, there are four obviousness objections at issue, and

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all of them turn principally upon the primary reference, which is the Patent

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to Edwards. And as a threshold issue, one of the difficulties in this case

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was, in my opinion, the legal standard that was applied, because the Patent

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Office had insisted on a showing of criticality between the claims and the

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prior art references. I think the correct legal standard was a showing of

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nonobviousness by the Patent Office in the first instance.

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Having said that, I think there's been a pretty basic misunderstanding

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of Edwards, primarily, and of what the claims actually encompass, and that's

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why I gave you those cartoons.

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In general, there are at least four primary differences between the

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claimed invention and Edwards and Edwards combined with any of the three

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secondary references. Those four differences are particle size, crystalline

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morphology, the aggregate shape, and the requirement that the dispersion

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returns to a nanoparticulate version.

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Starting with particle size, I'll refer you to the first page of the

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handout that simply shows in rather simplified but not distorted fashion that

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1 the claims really consist of the aggregates, are essentially a two- component
2 thing. The one, the macroscopic, is the respirable aggregate which has a
3 particle size of less than about 100 microns, and within each aggregate are
4 nanoparticulate drug particles which have a size of less than about 1 micron.

5 In contrast, the cited Edwards reference all along has been asserted to
6 teach the nanoparticulate size. Where I think the basic misunderstanding is,
7 that Edwards and any of the cited references fail to teach those two
8 component features of the claimed invention. Specifically, Edwards is
9 directed to respirable micronized drugs where the mean particle size is 5 to
10 30 microns, which is quite different than having aggregates of 100 microns
11 and drug particles on a nanoparticulate size scale.

12 Moreover, Edwards teaches away from the claimed invention. That's
13 because Edwards teaches it's not preferred to have very small particles, and
14 by very small Edwards means about five microns or less. The reason for this
15 is that phagocytes in the lungs will subject the smaller particles to
16 phagocytosis, which completely defeats the point of having respirable
17 particles.

18 Moreover, Edwards says that larger particles are preferred to
19 aerosolize the drug more efficiently. So based on that difference alone,
20 Edwards clearly teaches away from the claimed invention.

21 Moving to the second component, which is crystallinity, each of the
22 claims requires the drug to be present in a crystalline nanoparticulate form,
23 that is, the drug itself is a crystal. Now Edwards does not explicitly teach
24 whether the disclosed drug is crystalline or not. However, the methods
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1 disclosed in Edwards to make the respirable particles clearly gives rise to an
2 inference that the particles are amorphous, and this is because the methods
3 specifically disclosed are evaporation of the drug and/or, preferably, a spray
4 drying. Both these methods almost invariably give rise to amorphous drugs.

5 Moreover, Edwards says that the particles have pores or cavities.
6 They're porous, fluffy particles which are features completely inconsistent
7 with a crystalline drug particle. If you like, I'll give you specific cites, but
8 these are in my brief, too.

9 JUDGE GREEN: Can you give me a cite for the pores?

10 MR. REID: Certainly, in Column 5, Lines 64 through 67. So,
11 Edwards discusses different properties of a particle that contribute to
12 aerodynamic lightness. These include a regular surface structure, pores or
13 cavities within the particle.

14 Along the same access, the third primary difference between Edwards
15 and the claimed invention is the shape of the aggregate. These are the large
16 100-micron or less aggregates.

17 The claims require -- each of the claims require the aggregate to be
18 spherically shaped. Edwards takes a different tack: in fact, teaches exactly
19 the opposite. Edwards says that the aerodynamically light particles must be
20 rough, nonsmooth, and nonspherical. I'll refer you to Column 9, Lines 15
21 through 17 in Edwards.

22 Edwards, moreover, contemplates particles of any size or shape -- this
23 is the same Column 9, Lines 27 through 28 -- any size or any shape, and at
24 any event nonspherical is epithetical to spherical in the claims. Moreover,
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1 Edwards in describing the invention disclosed therein distinguishes that
2 invention from what it characterizes as prior art smooth and spherical micro-
3 particles. You'll find that discussion in Column 9, Lines 1 through 16.
4 Thus, it's clear that Edwards distinguishes self from prior art by
5 emphasizing nonspherical rough, nonsmooth particles contrast to the
6 claimed invention as well.

7 In the fourth and final difference, the technical difference between the
8 claimed invention and Edwards is the requirement in each claim that the
9 aggregate, when reconstituted in aqueous liquid medium, return, give rise to
10 the nanoparticulate dispersion from which the aggregates were made.

11 In Edwards, there can't -- there absolutely cannot be any return to a
12 nanoparticulate dispersion because there is none to begin with. Moreover,
13 Edwards nowhere discusses particles of nanoparticulate size, only
14 microparticles that are five microns or larger. And further, Edwards teaches
15 that the microparticles once in the lungs undergo slow degradation and drug
16 release to the lungs, which is not the same as a return to nanoparticulate
17 drug.

18 So I submit that based on these differences, Edwards clearly does not
19 teach or suggest all the elements of the claims. Moreover, Edwards clearly
20 teaches away from the claimed invention.

21 JUDGE GREEN: As to the secondary references, can you just discuss
22 Liversidge?

23 MR. REID: Sure.

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25

1 JUDGE GREEN: And just because that's the one that seemed to talk
2 about the nanoparticles --

3 MR. REID: Yes.

4 JUDGE GREEN: -- and the crystalline and everything else.

5 MR. REID: But Liversidge, as you may recognize, is co-owned by
6 the Applicant, the Assignee in this case. Liversidge is directed to
7 noninhalable forms of nanoparticulate drugs. Any drug -- the
8 nanoparticulate drug is crystalline and it has a surface modifier on each drug
9 particle. The Liversidge furthermore teaches that you can spray a dispersion
10 of the nanoparticulate drugs onto sugar spheres or an incipient. The key
11 distinction between Liversidge and this invention is that Liversidge does not
12 disclose or even suggest that these nanoparticles can be used in inhalable
13 forms. Specifically, Liversidge says that you can use these only in
14 parenteral or oral dosage forms, such as an intravenous delivery.

15 JUDGE GREEN: But does that cause any structural differences to the
16 composition? I mean, the fact that he doesn't disclose that they're not
17 inhalable doesn't mean that they couldn't be, so I'm just curious whether
18 there are structural differences.

19 MR. REID: The main technical structural difference or issue is
20 converting the liquid dispersion into a respirable aggregate as is claimed. So
21 at the time this application was filed, it was not known or even expected that
22 you could take a dispersion, a liquid dispersion of nanoparticles and convert
23 them into a respirable or inhalable form.

24

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1 JUDGE GREEN: So would that mean that Liversidge does not teach
2 the spherical particle aggregate to having about the size of 10 microns?

3 MR. REID: That's correct. In fact, the whole point of Liversidge was
4 to prevent aggregation of nanoparticulate drug.

5 JUDGE SCHEINER: You're saying that the nanoparticles are put
6 directly into suspension, they're not -- they're never aggregated?

7 MR. REID: That's correct. In fact, there is discussion in Liversidge
8 about the grinding of bulk drug into nanoparticles, and it's that resulting
9 dispersion which can be used immediately. The whole point of keeping a
10 dispersion with surface -- adhered surface modifiers is to prevent
11 aggregation of these nanoparticles into aggregates.

12 The aggregation was the main problem for respirable particles. When
13 its uncontrolled aggregation leads to unpredicted -- unpredictable aggregate
14 size -- and as you may know from the application, from the cited literature,
15 control of aggregate size is absolutely essential to targeting different parts of
16 the airway, be it the nasal airway or deep down the lung. Liversidge teaches
17 nothing whatsoever about aggregates or aggregate size.

18 Did that address your question completely?

19 JUDGE GREEN: Yes, it did. Thank you.

20 MR. REID: The third secondary reference is Dalby, which does not
21 address the limitations, the deficiencies of Edwards. Rather, Dalby is
22 concerned with aerosolized compositions of a specific drug, namely,
23 Beclomethasone. Dalby does not teach that the particles -- or does not
24 clearly teach the particles are aerosolized in a crystalline form.

25

1 Moreover, Dalby does not address the spherical aggregates that are
2 claimed and Dalby, furthermore, does not teach or suggest that aggregates if
3 formed can be reconstituted into nanoparticulate drug as the present claims
4 require. Moreover, Dalby teaches away again from the invention. This is
5 because Dalby strongly prefers the drug stays in solution. The reference
6 teaches this at discussion from Column 4, Line 59 through Column 5, Line
7 2.

8 Specifically, Dalby says the drug should stay in solution to prevent,
9 one, crystal growth problems; two, to maximize drug delivery; and third,
10 perhaps most important, to minimize oral pharynx deposition. And, these
11 three features that are encouraged by Dalby are apathetical to the presence of
12 crystalline drug nanoparticles as in the claims.

13 And, finally, the fourth reference is more or less a reference work,
14 Goodman and Gilmans, or the discussion of a particular drug administration
15 route. In any event, Goodman does not address any of the deficiencies I
16 highlighted earlier with Edwards, Liversige or Dalby.

17 So keep these clear-cut differences in mind, and with at least two of
18 main references teaching away from the invention, the claims are
19 nonobvious in light of these four references. Thank you.

20 JUDGE SCHEINER: Do you have anything further?

21 JUDGE GREEN: Nothing, thank you.

22 JUDGE SCHEINER: Thank you for coming in.

23 MR. REID: Quite welcome. Appreciate your time. Thank you.

24 (Whereupon, the hearing concluded on June 10, 2008.)

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